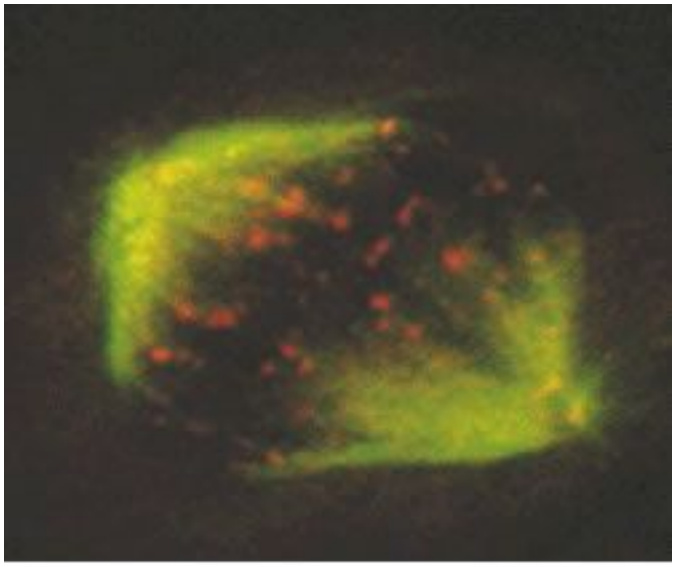
Cancers



An immortal HeLa cell, originally derived from a human tumor, undergoing cell division. It is stained with anti-tubulin (green) and anti-CENP-E (red) antibodies. CENP-E, a kinesin, is associated with the centromeres of paired sister chromatids during metaphase. [Photograph by Tim Yen and colleagues, Fox Chase Cancer Center, PA, USA. Reproduced from Endow, SE (1993) Trends Genet. 9, 52-55, with permission.]

Cancer occurs when cell division gets out of control. Usually, the timing of cell division is under strict constraint, involving a network of signals that work together to say when a cell can divide, how often it should happen and how errors can be fixed. Mutations in one or more of the nodes in this network can trigger cancer, be it through exposure to some environmental factor (e.g. tobacco smoke) or because of a genetic predisposition, or both. Usually, several cancer-promoting factors have to add up before a person will develop a malignant growth: with some exceptions, no one risk alone is sufficient.

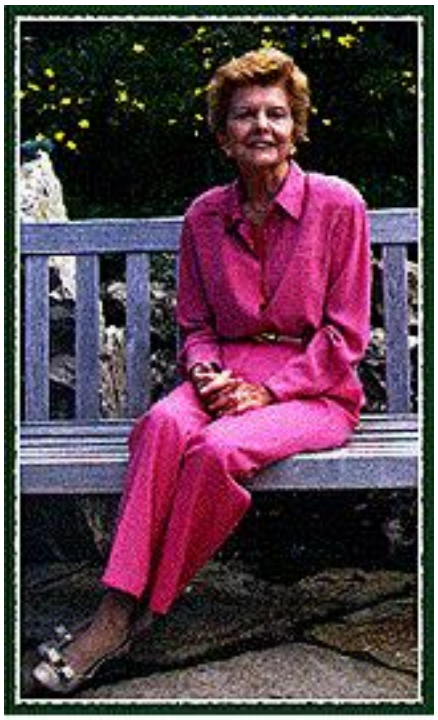
The predominant mechanisms for the cancers featured here are (i) impairment of a DNA repair pathway (ii) the transformation of a normal gene into an oncogene and (iii) the malfunction of a tumor supressor gene.

Breast and Ovarian Cancer

Breast cancer is the second major cause of cancer death in American women, with an estimated 44,190 lives lost (290 men and 43,900 women) in the US in 1997. While ovarian cancer accounts for fewer deaths than breast cancer, it still represents 4% of all female cancers. For some of the cases of both types of cancer, there is also a clear genetic link.

In 1994, two breast cancer susceptibility genes were identified: *BRCA1* on chromosome 17 and *BRCA2* on chromosome 13. When an individual carries a mutation in either *BRCA1* or *BRCA2*, they are at an increased risk of being diagnosed with breast or ovarian cancer at some point in their lives. Until recently, it was not clear what the function of these genes was, until studies on a related protein in yeast revealed their normal role: they participate in repairing radiation-induced breaks in double-stranded DNA. It is though that mutations in *BRCA1* or *BRCA2* might disable this mechanism, leading to more errors in DNA replication and ultimately to cancerous growth.

So far, the best opportunity to reduce mortality is through early detection (general screening of the population for *BRCA1* and *BRCA2* is not yet recommended). However, new strategies to find anti-cancer drugs are constantly being developed. The latest, called "synthetic lethal screening" looks for new drug targets in organisms such as yeast and fruit flies. In the same way that studies in yeast recently helped to identify the functions of BRCA1 and BRCA2, it is thought that drugs that work in more primative organisms will also be applicable to humans.



"While we all work toward a cure, education, research and increased access to treatment remain our best allies in the fight against breast cancer."

Betty Ford, former breast cancer patient and now an activist on behalf of expanded breast cancer research and education.

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=breast%20cancer] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=breast%20cancer&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=6552299&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=breast%20cancer%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=breast%20cancer] online books section

OMIM [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=omim&details_term=breast%20cancer] catalog of human genes and disorders

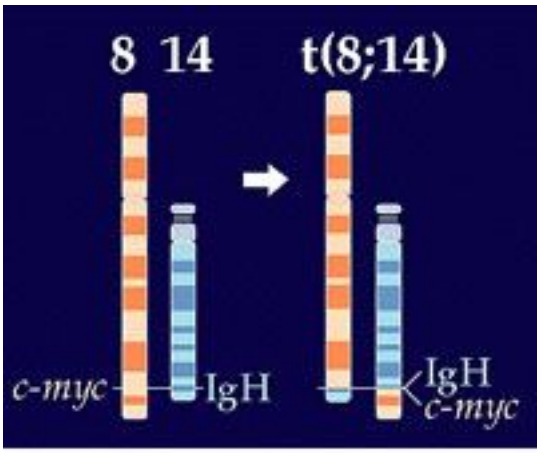
Websites

CancerNet [cancernet.nci.nih.gov/] from the National Cancer Institute, NIH

Oncolink [oncolink.upenn.edu/] comprehensive cancer information from the University of Pennsylvania

GeneClinics [www.geneclinics.org/profiles/brca1/index.html] a medical genetics resource

Burkitt Lymphoma



In Burkitt lymphoma, Myc, which is normally found on chromosome 8, is transferred to chromosome 14. This is known as chromosome translocation and can be characteristic of a cancer type. [image credit: Gregory Schuler, NCBI, NLM, NIH.]

Burkitt lymphoma is a rare form of cancer predominantly affecting young children in Central Africa, but the disease has also been reported in other areas. The form seen in Africa seems to be associated with infection by the Epstein–Barr virus, although the pathogenic mechanism is unclear.

Burkitt lymphoma results from chromosome translocations that involve the *Myc* gene. A chromosome translocation means that a chromosome is broken, which allows it to associate with parts of other chromosomes. The classic chromosome translocation in Burkitt lymophoma involves chromosome 8, the site of the *Myc* gene. This changes the pattern of *Myc*'s expression, thereby disrupting its usual function in controlling cell growth and proliferation.

We are still not sure what causes chromosome translocation. However, research in model organisms such as mice is leading us toward a better understanding of how translocations occur and, hopefully, how this process contributes to Burkitt lymphoma and other cancers such as leukemia.

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=myc%20OR%20burkitt%20lymphoma] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=burkitt%20lymphoma&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=12962935&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=burkitt%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=burkitt] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=PureSearch&db=omim&details_term=burkitt%20lymphoma] catalog of human genes and disorders

Websites

CancerNet [cancernet.nci.nih.gov/] from the National Cancer Institute, NIH

American Cancer Society [www.cancer.org/] research and patient support

Oncolink [oncolink.upenn.edu/] comprehensive cancer information from the University of Pennsylvania

Colon Cancer

The American Cancer Society estimates that there will be 93,800 new cases of colon cancer diagnosed in the US in 2000, with 47,700 resulting deaths. All kinds of cancer occur when cell division, normally a very highly regulated process, gets out of control. While environmental factors can certainly contribute to a person's risk of cancer (e.g. smoking, diet, and exercise), most cancers have a genetic basis too. Literally hundreds of genes and proteins are involved in monitoring the process of cell division and DNA replication; a mutation in one or more of these genes or proteins can sometimes lead to uncontrolled cancerous growth.

Colon cancer is one of the most common inherited cancer syndromes known. Among the genes found to be involved in colorectal cancer are: *MSH2* and *MSH6* both on chromosome 2 and *MLH1*, on chromosome 3. Normally, the protein products of these genes help to repair mistakes made in DNA replication. If the MSH2, MSH6, and MLH1 proteins are mutated and therefore don't work properly, the replication mistakes are not repaired, leading to damaged DNA and, in this case, colon cancer.

It is not clear why mutations in genes that are essential in all tissues preferentially cause cancer in the colon. However, studies on the equivalent genes in mice and brewer's yeast are helping to further our understanding of the mechanisms of DNA repair and the role that environmental factors might play in colon cancer incidence.

The human genes mutated in some colon cancers are homologous to enzymes in the DNA mismatch repair pathway in the E. coli bacterium (above) as well as yeast and mice.

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=colon%20cancer] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=colon%20cancer&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557761&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=colon%20cancer%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=colon%20cancer] online books section

OMIM [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=omim&details_term=colon%20cancer] catalog of human genes and disorders

Websites

CancerNet [cancernet.nci.nih.gov/] from the National Cancer Institute, NIH

American Cancer Society [www.cancer.org] research and patient support

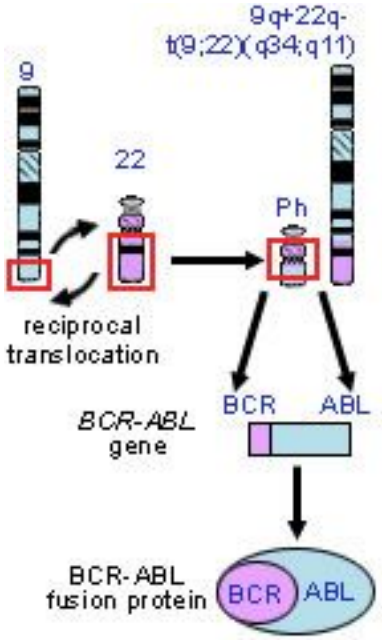
Oncolink [oncolink.upenn.edu/] comprehensive cancer information from the University of Pennsylvania

Leukemia, Chronic Myeloid

Chronic myeloid leukemia (CML) is a cancer of blood cells, characterized by replacement of the bone marrow with malignant, leukemic cells. Many of these leukemic cells can be found circulating in the blood and can cause enlargement of the spleen, liver, and other organs.

CML is usually diagnosed by finding a specific chromosomal abnormality called the Philadelphia (Ph) chromosome (see figure), named after the city where it was first recorded. The Ph chromosome is the result of a translocation—or exchange of genetic material—between the long arms of chromosomes 9 and 22 . This exchange brings together two genes: the *BCR* (breakpoint cluster region) gene on chromosome 22 and the proto-oncogene *ABL* (Ableson leukemia virus) on chromosome 9. The resulting hybrid gene *BCR-ABL* codes for a fusion protein with tyrosine kinase activity, which activates signal transduction pathways, leading to uncontrolled cell growth.

A mouse model has been created that develops a CML-like disease when given bone marrow cells infected with a virus containing the *BCR-ABL* gene. In other animal models, the fusion proteins have been shown to transform normal blood precursor cells to malignant cells. To research the human disease, antisense oligomers (short DNA segments) that block *BCR-ABL* were developed that specifically suppressed the formation of leukemic cells while not affecting the normal bone marrow cell development. These and other experimental techniques may lead to future treatments for CML.



Leukemic white blood cells in CML contain a Philadelphia (Ph) chromosome, the result of a translocation between the long arms of chromosomes 9 and 22. The resulting fusion gene (*BCR-ABL*) produces an altered protein believed to play a key role in the development of CML.

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=BCR%20OR%20ABL] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=BCR%20OR%20ABLa&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=11038639&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=BCR%20AND%20ABL%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=BCR%20AND%20ABL] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=PureSearch&db=omim&details_term=BCR%20OR%20ABL] catalog of human genes and disorders

Websites

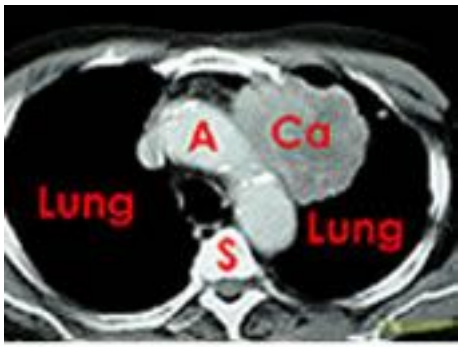
CancerNet [cancernet.nci.nih.gov/wyntk_pubs/leukemia.htm] from the National Cancer Institute, NIH

Lung Carcinoma, Small Cell

In the US, lung cancer is the most common cause of cancer deaths among both men and women. In fact, North Americans have the highest rates of lung cancer in the world. In 1997, some 178,100 new cases were diagnosed, and roughly 160,400 deaths occurred from the disease. Sadly, the 5-year survival rate for persons with lung cancer is only 14%. Since the 1940s, the increase in lung cancer mortality by gender has followed historic patterns of smoking, with a 20-year time lag. About 90% of male lung cancer deaths and 80% of female lung cancer deaths are attributable to cigarette smoking. Although smoking is by far the major risk factor for lung cancer, certain industrial substances, such as asbestos, and environmental factors can contribute.

Small cell lung carcinoma is distinctive from other kinds of lung cancer (metastases are already present at the time of discovery) and accounts for approximately 110,000 cancer diagnoses annually. A deletion of part of chromosome 3 was first observed in 1982 in small cell lung carcinoma cell lines.

As with other cancers, mutations in a variety of molecules (oncogenes and tumor-suppressor genes) that control cell growth and division are observed, and no one mutation is likely to result in cancerous growth. Basic research into the function of these molecules—how and when they play their role—should help the fight against lung, and other, cancers and give clues to find appropriate therapies.



CT scan showing lung cancer. [Image credit: Pat Connelly, Miami Valley Hospital, Dayton, OH, USA.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=lung+cancer] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=lung+cancer&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4826696&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=lung+cancer%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=lung+cancer] online books section

OMIM [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=omim&details_term=lung+cancer] catalog of human genes and disorders

Websites

CancerNet [cancernet.nci.nih.gov/] from the National Cancer Institute, NIH

American Cancer Society [www.cancer.org] research and patient support

Oncolink [oncolink.upenn.edu/] comprehensive cancer information from the University of Pennsylvania

Malignant Melanoma

In 1997, it was expected that about 40,300 Americans would be diagnosed with malignant melanoma, the most aggressive kind of skin cancer. Melanomas are more common in people with lightly pigmented skin, and people who have had melanoma once have a high risk of developing new melanomas.

In some cases, the risk of developing melanoma runs in families, where a mutation in the *CDKN2* gene on chromosome 9 can underlie susceptibility to melanoma. *CDKN2* codes for a protein called p16 that is an important regulator of the cell division cycle; it stops the cell from synthesizing DNA before it divides. If p16 is not working properly, the skin cell does not have this brake on the cell division cycle and so can go on to proliferate unchecked. At some point this proliferation can be seen as a sudden change in skin growth or the appearance of a mole.

The most powerful weapons against melanoma are therefore 1) prevention, by using protective clothing and sun screen and 2) early detection, by recognizing changes in skin growths or the appearance of new growths. Insight may also be drawn for other cancer types by studying the molecular biology of p16, since the malfunction of other components of the p16 pathway have also been implicated in other cancers.

Malignant melanoma is associated with mutation of a tumor suppressor gene involved in cell cycle control. [Image credit: National Cancer Institute, NIH, Bethesda, MD, USA .]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=melanoma] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=malignant%20melanoma&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4502749&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=malignant%20melanoma%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=melanoma] online books section

OMIM [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=omim&details_term=malignant%20melanoma] catalog of human genes and disorders

Websites

CancerNet [cancernet.nci.nih.gov/] from the National Cancer Institute, NIH

American Cancer Society [www.cancer.org] research and patient support

MEDLINE *plus* [www.nlm.nih.gov/medlineplus/melanoma.html] links on melanoma compiled by the National Library of Medicine

Multiple Endocrine Neoplasia

Multiple endocrine neoplasia (MEN) is a group of rare diseases caused by genetic defects that lead to hyperplasia (abnormal multiplication or increase in the number of normal cells in normal arrangement in a tissue) and hyperfunction (excessive functioning) of two or more components of the endocrine system.

Endocrine glands are different from other organs in the body because they release hormones into the bloodstream. Hormones are powerful chemicals that travel through the blood, controlling and instructing the functions of various organs. Normally, the hormones released by endocrine glands are carefully balanced to met the body's needs. When a person has MEN, specific endocrine glands, such as the parathyroid glands, the pancreas gland, and the pituitary gland, tend to become overactive. When these glands go into overdrive, the result can be: excessive calcium in the bloodstream (resulting in kidney stones or kidney damage); fatigue; weakness; muscle or bone pain; constipation; indigestion; and thinning of bones.

The MEN1 gene, which has been known for several years to be found on chromosome 11, was more finely mapped in 1997.

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=multiple+endocrine+neoplasia] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=multiple+endocrine+neoplasia&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557745&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=multiple+endocrine+neoplasia%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=multiple+endocrine+neoplasia] online books section

OMIM [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=omim&details_term=multiple+endocrine+neoplasia] catalog of human genes and disorders

Websites

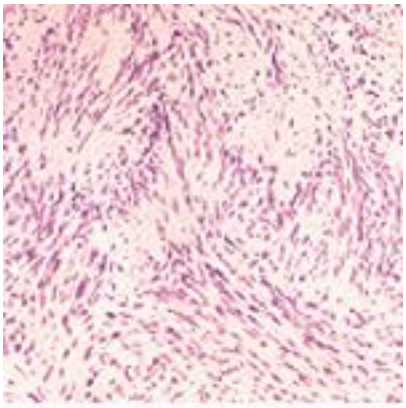
Fact sheet [www.niddk.nih.gov/health/endo/pubs/fmen1/fmen1.htm] from the National Institute of Diabetes and Digestive and Kidney Diseases, NIH

Neurofibromatosis

Neurofibromatosis, type 2, (NF-2) is a rare inherited disorder characterized by the development of benign tumors on both auditory nerves (acoustic neuromas). The disease is also characterized by the development of malignant central nervous system tumors as well.

The NF2 gene has been mapped to chromosome 22 and is thought to be a so-called 'tumor-suppressor gene'. Like other tumor suppressor genes (such as p53 and Rb), the normal function of NF2 is to act as a brake on cell growth and division, ensuring that cells do not divide uncontrollably, as they do in tumors. A mutation in NF2 impairs its function, and accounts for the clinical symptoms observed in neurofibromatosis sufferers. NF-2 is an autosomal dominant genetic trait, meaning it affects both genders equally and that each child of an affected parent has a 50% chance of inheriting the gene.

We are learning more about the function of the NF2 gene through studies of families with neurofibromatosis type 2 and through work in model organisms, particularly mice. The exact molecular function of NF2 in the cell is still unknown, although the protein is similar to the ERM family of cytoskeleton-membrane linker proteins. Further work on the binding partners of NF2 would help to identify potential specific targets for future drug therapies.



Microscopic section of a schwannoma, a tumor commonly found in patients with NF-2. [Image credit: K Roth and Robert Schmidt, Washington University, St. Louis, MO, USA.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=neurofibromatosis] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=neurofibromatosis&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557793&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=neurofibromatosis%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=neurofibromatosis] online books section

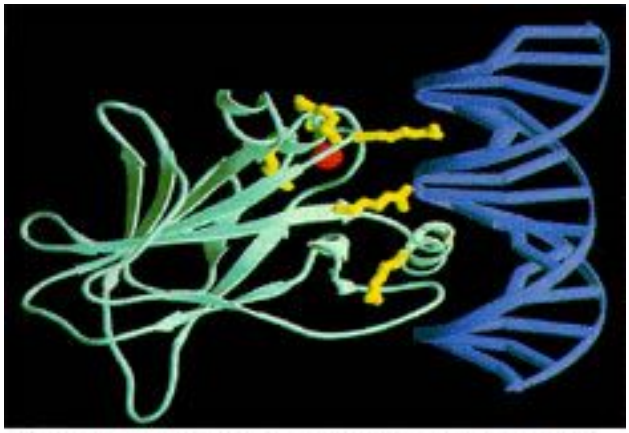
OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=101000] catalog of human genes and disorders

The p53 Tumor Suppressor Protein

The p53 gene like the Rb gene, is a tumor suppressor gene, i.e., its activity stops the formation of tumors. If a person inherits only one functional copy of the p53 gene from their parents, they are predisposed to cancer and usually develop several independent tumors in a variety of tissues in early adulthood. This condition is rare, and is known as Li-Fraumeni syndrome. However, mutations in p53 are found in most tumor types, and so contribute to the complex network of molecular events leading to tumor formation.

The p53 gene has been mapped to chromosome 17. In the cell, p53 protein binds DNA, which in turn stimulates another gene to produce a protein called p21 that interacts with a cell division-stimulating protein (cdk2). When p21 is complexed with cdk2 the cell cannot pass through to the next stage of cell division. Mutant p53 can no longer bind DNA in an effective way, and as a consequence the p21 protein is not made available to act as the 'stop signal' for cell division. Thus cells divide uncontrollably, and form tumors.

Help with unraveling the molecular mechanisms of cancerous growth has come from the use of mice as models for human cancer, in which powerful 'gene knockout' techniques can be used. The amount of information that exists on all aspects of p53 normal function and mutant expression in human cancers is now vast, reflecting its key role in the pathogenesis of human cancers. It is clear that p53 is just one component of a network of events that culminate in tumor formation.



The structure of the core domain of the p53 protein (light blue) bound to DNA (dark blue) The six most frequently mutated amino acids in human cancers are shown in yellow - all are residues important for p53 binding to DNA. Red ball: zinc atom. [Reproduced from Cho, Y., et al. (1994) Science, 265, 346-355, with kind permission.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=p53] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=p53&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=8400738&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=p53%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=p53] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=191170] catalog of human genes and disorders

Websites

CancerNet [cancernet.nci.nih.gov/] from the National Cancer Institute, NIH

Oncolink [oncolink.upenn.edu/] comprehensive cancer information from the University of Pennsylvania

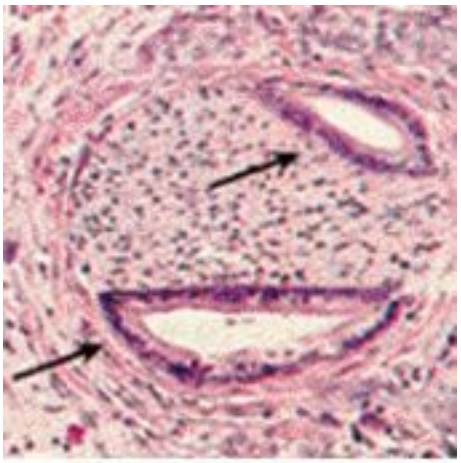
American Cancer Society [www.cancer.org] research and patient support

Pancreatic Cancer

The pancreas is responsible for producing the hormone insulin, along with other substances. It also plays a key role in the digestion of protein. There were an estimated 27,000 new cases of pancreatic cancer in the US in 1997, with 28,100 deaths from the disease.

About 90% of human pancreatic carcinomas show a loss of part of chromosome 18. In 1996, a possible tumor suppressor gene, DPC4 (Smad4), was discovered from the section that is lost in pancreatic cancer, so may play a role in pancreatic cancer. There is a whole family of Smad proteins in vertebrates, all involved in signal transduction of transforming growth factor β (TGFβ) related pathways. Other tumor suppressor genes include p53 and Rb, which, if mutated or absent from the genome can contribute to cancerous growth in a variety of tissues.

DPC4 (Smad4) homologs exist in the worm (*Caenorhabditis elegans*), mouse and the fly (*Drosophila*). In *Drosophila*, when the gene is not present, there a number of developmental defects. Likewise, homozygous Smad4 mutant mouse embryos die before embryonic day 7.5, and have reduced size because of reduced cell proliferation. Research on these model organisms should help elucidate the role of Smad4 and related proteins in humans.



Loss of DPC4 (Smad4) gene causes pancreatic cancers to grow aggressively, as seen by tumor cells invading a nerve bundle. [Image credit: R.H. Hruban, Johns Hopkins University, Baltimore, MD, USA. Reprinted from SCIENCE, with permission.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=pancreatic+cancer] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=pancreatic+cancer&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4885457&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=pancreatic+cancer%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=pancreatic+cancer] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=PureSearch&db=omim&details_term=pancreatic%20cancer] catalog of human genes and disorders

Websites

CancerNet [cancernet.nci.nih.gov/] from the National Cancer Institute, NIH

Oncolink [oncolink.upenn.edu/] comprehensive cancer information from the University of Pennsylvania

American Cancer Society [www.cancer.org] research and patient support

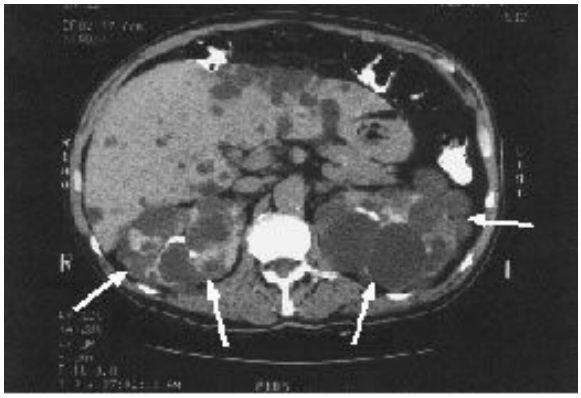
MEDLINE*plus* [www.nlm.nih.gov/medlineplus/pancreaticcancer.html] links on pancreatic cancer compiled by the National Library of Medicine

Polycystic Kidney Disease

Adult polycystic kidney disease (APKD) is characterized by large cysts in one or both kidneys and a gradual loss of normal kidney tissue which can lead to chronic renal failure. The role of the kidneys in the body is to filter the blood, excreting the end-products of metabolism in the form of urine and regulating the concentrations of hydrogen, sodium, potassium, phosphate and other ions in the extracellular fluid.

In 1994 the European Polycystic Kidney Disease Consortium isolated a gene from chromosome 16 that was disrupted in a family with APCD. The protein encoded by the PKD1 gene is an integral membrane protein involved in cell-cell interactions and cell-matrix interactions. The role of PKD1 in the normal cell may be linked to microtubule-mediated functions, such as the placement of Na(+), K(+)-ATPase ion pumps in the membrane. Programmed cell death, or apoptosis, may also be invoked in APKD. Further clarification of the pathogenesis of the disease await further research.

The so-called 'cpk mouse' is a well known model for the human disease. Studying the molecular basis of the disease in the mouse is expected to provide a better understanding of the human disease, and is hoped to lead to more effective therapies.



Contrast-enhanced abdominal computed tomography showing kidneys (arrows) containing numerous cystic masses. [Reproduced with permission from Fred, H.L. and Siddique, I. (1995) New Eng. J. Med. 333, 31.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=polycystic+kidney+disease] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=polycystic+kidney+disease&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4505833&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=polycystic+kidney+disease%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=polycystic+kidney+disease] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=173900] catalog of human genes and disorders

Websites

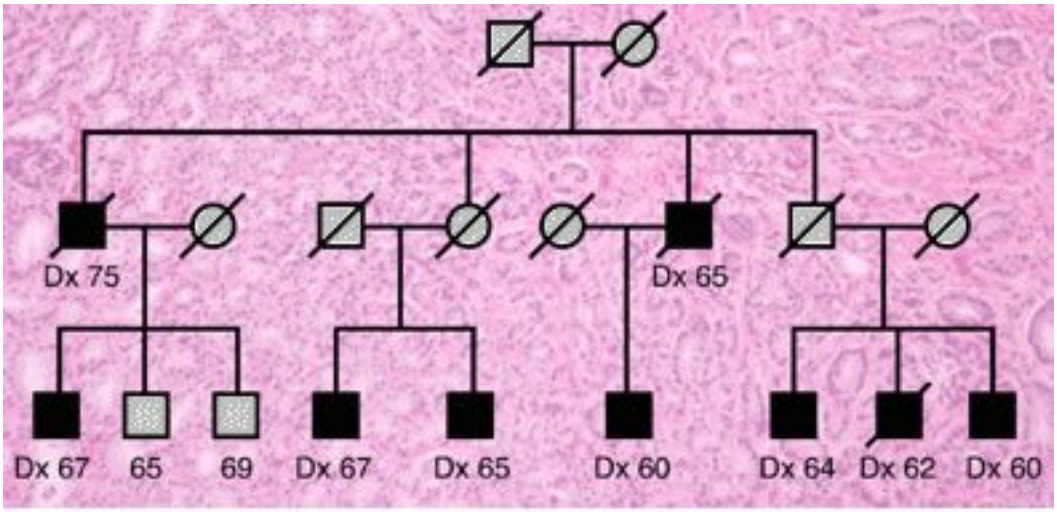
Fact sheet [www.niddk.nih.gov/health/kidney/pubs/polycyst/polycyst.htm] from the National Institute of Diabetes and Digestive and Kidney Diseases, NIH

Prostate Cancer

The second leading cause of cancer death in American men, prostate cancer will be diagnosed in an estimated 184,500 American men in 1998 and will claim the lives of an estimated 39,200. Prostate cancer mortality rates are more than two times higher for African-American men than white men. The incidence of prostate cancer increases with age; more than 75% of all prostate cancers are diagnosed in men over age 65.

Despite the high prevalence of prostate cancer, little is known about the genetic predisposition of some men to the disease. Numerous studies point to a family history being a major risk factor, which may be responsible for an estimated 5-10% of all prostate cancers.

One of the most promising recent breakthroughs may be the discovery of a susceptibility locus for prostate cancer on chromosome 1, called HPC1, which may account for about 1 in 500 cases of prostate cancer. The next step will be to clone the gene. Once researchers have the sequence, they will be able to search the databases to compare the HPC1 sequence to previously characterized proteins from both humans and other animals. This should provide clues as to the function of HPC1 in the cell, and suggest potential starting points to find drug targets.



Hereditary prostate cancer (HPC) accounts for about 10% of all prostate cancer, and HPC1 is estimated to account for approximately 34% of these hereditary cases. Background: histological section of a patient with HPC. Foreground: pedigree of a typical family demonstrating multiple affected individuals (solid boxes) whose disease links to the HPC1 region on chromosome 1. [With thanks to Jeffrey Trent and colleagues, NIHGR, NIH, for supplying the image.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=prostate%20cancer] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=prostate%20cancer&ORG=Hs&V=0] collection of gene-related information

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=prostate%20cancer%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=prostate%20cancer] online books section

OMIM [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=omim&details_term=prostate%20cancer] catalog of human genes and disorders

Websites

Fact sheet [www.nhgri.nih.gov/DIR/LCG/PROSTATE/pros_home.html] from the National Human Genome Research Institute, NIH

CancerNet [cancernet.nci.nih.gov/] from the National Cancer Institute, NIH

Oncolink [oncolink.upenn.edu/] comprehensive cancer information from the University of Pennsylvania

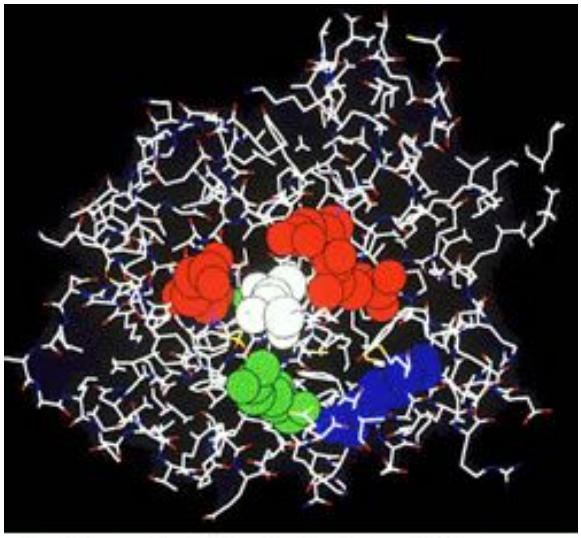
GeneClinics [www.geneclinics.org/profiles/brca1/index.html] a medical genetics resource

Harvey Ras Oncogene

Cancer occurs when the growth and differentiation of cells in a body tissue become uncontrolled and deranged. While no two cancers are genetically identical (even in the same tissue type), there are relatively few ways in which normal cell growth can go wrong. One of these is to make a gene that stimulates cell growth hyperactive; this altered gene is known as an 'oncogene'.

Ras is one such oncogene product that is found on chromosome 11. It is found in normal cells, where it helps to relay signals by acting as a switch. When receptors on the cell surface are stimulated (by a hormone, for example), Ras is switched on and transduces signals that tell the cell to grow. If the cell-surface receptor is not stimulated, Ras is not activated and so the pathway that results in cell growth is not initiated. In about 30% of human cancers, Ras is mutated so that it is permanently switched on, telling the cell to grow regardless of whether receptors on the cell surface are activated or not.

Usually, a single oncogene is not enough to turn a normal cell into a cancer cell, and many mutations in a number of different genes may be required to make a cell cancerous. To help unravel the intricate network of events that lead to cancer, mice are being used to model the human disease, which will further our understanding and help to identify possible targets for new drugs and therapies.



The three-dimensional structure of Ras protein. Many of the mutations of Ras observed in human cancers have been pin-pointed and mapped onto this structure. [Image credit: Mark Boguski, NCBI, NIH, Bethesda, USA.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=hras] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=hras&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4885425&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=ras%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=ras] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=190020] catalog of human genes and disorders

Retinoblastoma

Retinoblastoma occurs in early childhood and affects about 1 child in 20,000. The tumor develops from the immature retina - the part of the eye responsible for detecting light and color. There are both hereditary and non-hereditary forms of retinoblastoma. IN the hereditary form, multiple tumors are found in both eyes, while in the non-hereditary form only one eye is effected and by only one tumor.

In the hereditary form, a gene called Rb is lost from chromosome 13. Since the absence of Rb seemed to be linked to retinoblastoma, it has been suggested that the role of Rb in normal cells is to suppress tumor formation. Rb is found in all cells of the body, where under normal conditions it acts as a brake on the cell division cycle by preventing certain regulatory proteins from triggering DNA replication. If Rb is missing, a cell can replicate itself over and over in an uncontrolled manner, resulting in tumor formation.

Untreated, retinoblastoma is almost uniformly fatal, but with early diagnosis and modern methods of treatment the survival rate is over 90%. Since the Rb gene is found in all cell types, studying the molecular mechanism of tumor suppression by Rb will give insight into the progression of many types of cancer, not just retinoblastoma.

A complex of retinoblastoma protein (RB) with E7 - a viral oncoprotein that frequently binds to RB and blocks its function in cervical cancer. The degree of green color shows the conservation of amino acids in RB and related proteins. [Reproduced from Lee, J-O., Russo, A.A. and Pavletich, N.P. (1998) Nature 391, 859-865, with permission.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=retinoblastoma] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=RB1&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4506435&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=retinoblastoma%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=retinoblastoma] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=180200] catalog of human genes and disorders

Websites

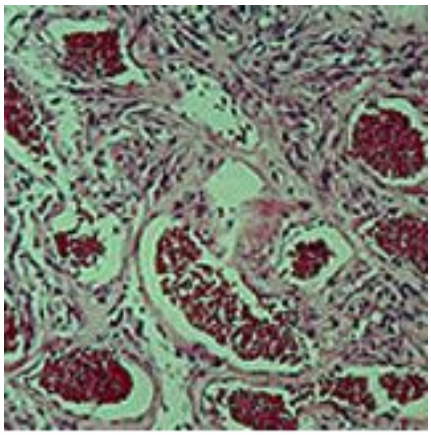
The National Eye Institute, NIH [www.nei.nih.gov/] research and patient information

Tuberous Sclerosis

Tuberous sclerosis is an hereditary disorder characterized by benign, tumor-like nodules of the brain and/or retinas, skin lesions, seizures and/or mental retardation. Patients may experience a few or all of the symptoms with varying degrees of severity.

Two loci for tuberous sclerosis have been found: TSC1 on chromosome 9, and TSC2 on chromosome 16. It took four years to pin down a specific gene from the TSC1 region of chromosome 9: in 1997, a promising candidate was found. Called hamartin by the discoverers, it is similar to a yeast protein of unknown function, and appears to act as a tumor suppressor: without TSC1, growth of cells proceeds in an unregulated fashion, resulting in tumor formation. TSC2 codes for a protein called tuberin, which, through database searches, was found to have a region of homology to a protein found in pathways that regulate the cell (GAP3, a GTPase-activation protein).

SC1 has a homolog in yeast, which provides a system in which to model the human disease.



Microscopic section of angiomyolipoma, a benign tumor of the kidney present in many patients with tuberous sclerosis. [Image credit: Moyra Smith, Johns Hopkins University, Baltimore, MD, USA.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=tuberous+sclerosis] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=tuberous+sclerosis&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4507693&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=tuberous+sclerosis%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=tuberous+sclerosis] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=191100] catalog of human genes and disorders

Websites

CancerNet [cancernet.nci.nih.gov/] from the National Cancer Institute, NIH

Oncolink [oncolink.upenn.edu/] comprehensive cancer information from the University of Pennsylvania

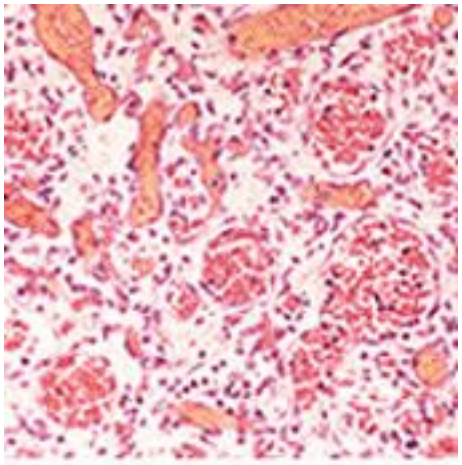
GeneClinics [www.geneclinics.org/profiles/brca1/index.html] a medical genetics resource

Von Hippel-Lindau Syndrome

Von Hippel-Lindau syndrome is an inherited multi-system disorder characterized by abnormal growth of blood vessels. While blood vessels normally grow like trees, in people with VHL little knots of blood capillaries sometimes occur. These knots are called angiomas or hemangioblastomas. Growths may develop in the retina, certain areas of the brain, the spinal cord, the adrenal glands and other parts of the body.

The gene for Von-Hippel Lindau disease (VHL) is found on chromosome 3, and is inherited in a dominant fashion. If one parent has a dominant gene, each child has a 50-50 chance of inheriting that gene. The VHL gene is a tumor suppressor gene. This means that its role in a normal cell is to stop uncontrolled growth and proliferation. If the gene is lost or mutated, then its inhibitory effect on cell growth is lost or diminished, which, in combination with defects in other regulatory proteins, can lead to cancerous growth. LIke the Rb tumor suppressor gene, VHL seems to act as a 'gatekeeper' to the multistep process of tumorigenesis.

Although unrelated to any other known family of human proteins, homologs to human VHL are found in mice and rats. Experiments using these animals as model organisms for the human disease are helping researchers discover the normal physiological role of VHL, which will shed light on its mechanism of pathogenesis. Initial results suggest that VHL may play a role in regulating exit form the cell cycle.



Microscopic section of hemangioblastoma, a tumor of the cerebellum characteriztically found in patients with von Hippel-Lindau disease. [Image credit: Kevin Roth and Robert Schmidt, Washington University, St. Louis, MO, USA.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=VHL] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=VHL&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4507891&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=Von-Hippel+Lindau%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=VHL] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=193300] catalog of human genes and disorders

Websites

Fact sheet [www.ninds.nih.gov/health_and_medical/disorders/vonhippe_doc.htm] from the National Institute of Neurological Disorders and Stroke, NIH